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10/550,788	11/16/2005	Seishi Kato	2005_1542A	1447

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Washington, DC 20005-1503

EXAMINER
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WILDER, CYNTHIA B

ART UNIT	PAPER NUMBER
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1637

NOTIFICATION DATE	DELIVERY MODE
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04/11/2011

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/550,788	<b>Applicant(s)</b> KATO ET AL.	
	<b>Examiner</b> CYNTHIA WILDER	<b>Art Unit</b> 1637	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 31 January 2011.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-5,7,11,13-17 and 19 is/are pending in the application.
- 4a) Of the above claim(s) 11,13-17 and 19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5 and 7 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                    | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)         | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

1. Applicant's amendment filed 1/31/2011 is acknowledged and has been entered. Claim 1-5, 7, 11, 13-17 and 19 are pending. Claims 11, 13-17 and withdrawn from consideration as being drawn to a non-elected invention. Claims 1-5 and 7 are discussed in this Office action. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

**This action is made FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### **Previous Rejections**

3. The prior art rejection under 5 USC 103(a) directed to claims 1-5 and 7 as being unpatentable over Chenchik et al in view of Brennan et al is maintained and discussed below. The prior art rejection under 35 US 103(a) directed to claims 1-5 and 7 as being unpatentable over Okayama et al in view of Brennan et al is maintained and discussed below.

### ***Claim Rejections - 35 USC § 103***

4. It is noted that the cited prior art is deemed acceptable prior art because Applicant has not filed a translation of the prior document filed 3/29/2004). Claims 1-5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chenchik et al (5962271, citation made of record in prior Office action) in view of Brennan et al

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(Methods in Enzymology, vol. 100, pages 38-52, 1983). Regarding claim 1, Chenchik et al teach a method comprising the steps of: (i) annealing a double-stranded DNA primer and an mRNA mixture, (ii) preparing an mRNA/cDNA heteroduplex by synthesizing the first-strand cDNA primed with the double-stranded DNA primer using reverse transcriptase, wherein the 3' end nucleotide of the first strand cDNA comprise an anchor (see for example Figure 1), (iii) circularizing the mRNA/cDNA heteroduplex by joining the 3' and 5' ends of the DNA strand containing cDNA using ligase and replacing the RNA in the mRNA/cDNA heteroduplex with the second strand cDNA thereby synthesizing the cDNA (see figure 4-1 and 4-2, col. 3-5, 7-9 and Examples; see also col. 8, line 61 to col. 9, line 13) possessing the 5' end nucleotide cap structure comprising the formula  $dN_1-dN_2-...dN_m-rN_1-rN_2-...rN_n$ , wherein dN represents a deoxyribonucleotide selected from among dAMP, dCMP, dGMP and dTMP; m represents an integer 0 and above, preferably from 10-50; rN represents a ribonucleotide selected from among AMP, CMP, GMP and UMP, preferably GMP; and n represents an integer 0 and above, preferably from 3 to 7 (col. 3, line 50 to col. 4, line 50).

Chenchik et al do not teach wherein the ligase is T4 RNA ligase, but rather wherein the ligase is T4 DNA ligase.

Brennan et al provide a general teaching T4 RNA ligases. Brennan et al teach that although RNA ligases uses oligoribonucleotides much more efficiently than oligodeoxyribonucleotides, short DNA oligomers can be both circularized and joined intermolecularly (page 39, second paragraph).

Kato supports the teachings of Brennan by disclosing wherein T4 RNA ligase is used for ligation of DNA-RNA chimeric oligonucleotide to mRNA (col. 3, lines 47-64).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention to substitute T4 RNA ligase as taught by Brennan and Kato in the place of the T4 DNA ligase in the synthesis method of Chenchik since the ordinary artisan has good reasons to peruse the known options within his or her technical grasp and further since the use of T4 RNA ligase does not negatively alter, modify or disrupt the method of synthesis method of Chenchik. In turn, because T4 RNA ligase is known to ligate DNA oligonucleotides, RNA oligonucleotides or chimeric oligonucleotides comprising RNA-DNA to mRNA as taught by Brennan and Kato, one of ordinary skill in the art at the time of the claimed invention could predictably expect a reasonable expectation of success in the DNA synthesis method of Chenchik.

Regarding claim 2, Chenchik et al teach that the small amount of total RNA from 10-50 mg of "difficult" cells or tissues, like human biopsy tissues, pathogenic microorganisms, and tissues at different development stages and so on (col. 11, lines 32-35). One of ordinary skill in the art at the time of the claimed invention would have a reasonable expectation of success in obtaining mRNA contained in a cell extract for use in methods of synthesizing cDNA possessing a cap structured based on the teachings of Chenchik et al. It would have been *prima facie* obvious over the cited prior arts in the absence of secondary consideration.

Regarding claim 3, Chenchik et al teach the method of claim 1, wherein mRNA possessing a cap structure is synthesized by in vitro transcription (col. 5, lines 11-53, and claim 1).

Regarding claim 4, Chenchik et al teach the method of claim 1, wherein the primer sequence of the double-stranded DNA primer contains a sequence complementary to a partial sequence of mRNA possessing a cap structure (see col. 7, line 52 to col. 8, line 43).

Regarding claim 5, Chenchik et al teach the method of claim 1, wherein the primer sequence of the double-stranded DNA primer contains an oligo dT complementary to a poly(A) sequence of mRNA possessing a cap structure (col. 7, lines 50-56).

Regarding claim 7, Chenchik et al teach the method of claim 1, which comprises the following step between the step (ii) and the step (iii): (ii') generating a 5'-protruding end or a blunt end at the terminal of the double-stranded DNA primer by cutting the conjugate of the mRNA/cDNA heteroduplex and the double-stranded DNA primer using a restriction enzyme (col. 11, Example 2).

### ***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 1-5 and 7 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Okayama et al (Molecular and Cellular Biology, Feb 1982; citation made of record) in view of Brennan et al (Methods in Enzymology, vol. 100, pages 38-52, 1983). Regarding claim 1, Okayama et al teach a method comprising the steps of: (i) annealing a double-stranded DNA primer and an mRNA mixture, (ii) preparing an mRNA/cDNA heteroduplex by synthesizing the first-strand cDNA primed with the double-stranded DNA primer using reverse transcriptase, (iii) circularizing the mRNA/cDNA heteroduplex by ligating the 5' end of the vector primer to the 3' end of the cDNA using a DNA ligase and replacing the RNA in the mRNA/cDNA heteroduplex with the second strand cDNA thereby synthesizing the cDNA (see figures 1 and 2 and pages 162-165)

Okayama et al do not expressly teach wherein the DNA ligase is a T4 RNA ligase. However, the art teaches that while T4 ligase is preferable for ligating RNA species, it can be use to ligate DNA molecules.

For example, Brennan et al provide a general teaching T4 RNA ligases. Brennan et al teach that although RNA ligases uses oligoribonucleotides much more efficiently than oligodeoxyribonucleotides, short DNA oligomers can be both circularized and joined intermolecularly (page 39, second paragraph).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention to substitute T4 RNA ligase as taught by Brennan and in the place of the T4 DNA ligase in the synthesis method of Okayama et al, since the

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ordinary artisan has good reasons to peruse the known options within his or her technical grasp and further since the use of T4 RNA ligase does not negatively alter, modify or disrupt the method of synthesis method of Okayama et al. In turn, because T4 RNA ligase is known to ligate DNA oligonucleotides, RNA oligonucleotides or chimeric oligonucleotides comprising RNA-DNA to mRNA as taught by Brennan, one of ordinary skill in the art at the time of the claimed invention could predictably expect a reasonable expectation of success in the DNA synthesis method of Okayama et al.

Regarding claim 2, Okayama et al teach wherein the mRNA is contained in a cell lysate (page 7, col. 1).

Regarding claim 3, Okayama et al teach the method of claim 1, wherein mRNA is synthesized by in vitro transcription (see materials and Methods, pages 152-164)

Regarding claim 4, Okayama et al teach the method of claim 1, wherein the primer sequence of the double-stranded DNA primer contains a sequence complementary to a partial sequence of mRNA (see Figure 1 and 2).

Regarding claim 5, Okayama et al teach the method of claim 1, wherein the primer sequence of the double-stranded DNA primer contains an oligo dT complementary to a poly(A) sequence of the mRNA (see figure 2).

Regarding claim 7, Okayama et al teach the method of claim 1, which comprises the following step between the step (ii) and the step (iii): (ii') generating a 5'-protruding end or a blunt end at the terminal of the double-stranded DNA primer by cutting the

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conjugate of the mRNA/cDNA heteroduplex and the double-stranded DNA primer using a restriction enzyme (see pages 162-165 and Figures 1 and 2).

### **Response to Arguments**

4. Applicant traverses the rejection on the following grounds: Applicant traverses the rejection on the grounds that one could not substitute the T4 RNA ligase of Brennan into the method of Chenchik et al or Okayama et al because the references do not teach wherein the use of T4 ligase is used for ligation of double stranded DNAs. Applicant states that the Brennan describes a short DNA oligomer can be circularized and joined intermolecularly, Applicant states that the Examiner refers to a second paragraph of page 39 of Brennan et al. However the Examiner is directed to the second sentence of this paragraph:

"We have found conditions under which 2'-deoxyribonucleotised 3'-biophosphates can be added to DNA oligomers and single stranded DNA oligomers be joined in good yields."

Applicant states that such sentence therefore indicates that single stranded DNA can be joined in good yield. Such is not a teaching of joining a double stranded DNA to a cDNA/mRNA heteroduplex as required in the claimed invention. Applicant states that the presented invention is based on the circularization of a mRNA/cDNA heteroduplex using T4 RNA ligase. Applicant reminds the Examiner that the heteroduplex is a double-stranded form and further one end of the heteroduplex is double-stranded DNA. Applicant states that the presented invention was completed by a finding that heteroduplex can be circularized by T4 RNA ligase rather than DNA ligase

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5. All of the arguments have been thoroughly reviewed and considered, but are not found persuasive for the reasons that follow: In response to Applicant's arguments, the examiner maintains that while the art and Brennan has established that T4 RNA ligase is not a preferred option for ligating DNA, it does not exclude the fact that T4 RNA ligase can be use to ligate DNA to DNA. Brennan clearly establishes this fact in the teaching short DNA oligomers can be both circularized and joined intermolecularly (page 39). The sentence noted by Applicant in Brennan et al does not establish that double stranded DNA is incapable of being circularized by an RNA ligase, rather it only established a DNA oligomer (which can be double stranded) and single stranded DNA oligomer (instead of a double stranded DNA oligomer) can be joined in good yield. A DNA oligomer without reference to it being "single stranded" is interpreted to mean that the DNA is "double strand. The Examiner maintains that Brennan provides clear evidence that an RNA ligase can be used to join DNA molecules. Brennan teaches conditions for DNA joining as states at page 44 the following:

Reaction conditions that differ from those usually used to join RNA molecules are required to enable DNA acceptors to serve and substrates with RNA ligase. The essential features are that higher enzyme and oligonucleotide concentrations are required, longer reaction times are necessary, incubation at low temperature is imperative, ATP concentrations must be maintained at low values and Mn(II) must be present.

Thus while Brennan concludes that it is difficult to used DNA acceptors with RNA, it is not impossible and further provides reaction conditions for doing so. Brennan therefore, provides a reasonable expectation of success for carrying out the invention using RNA ligase rather than a DNA ligase to join DNA molecules. Again, Applicant provides no evidence to support the conclusion that one could not use a RNA ligase in a method for

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joining DNA molecules. Further Applicant provides no evidence to contradict the conclusion that a DNA oligomer as taught by Brennan is not double stranded. Therefore, the Examiner maintains that a *prima facie* case of obviousness has been established against the rejected claims.

### ***Conclusion***

6. No claims are allowed. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gary Benzion/

Supervisory Patent Examiner, Art Unit 1637